REMARKS

Status of the claims

Claims 1, 6-12, 15, 19-25, and 28 are pending. Claims 1, 6-12, 15, 19-25, and 28 are rejected. Claims 1 and 15 are amended herein. Claims 2-5, 13-14, 16-18, 26-27 were canceled previously.

Amendments to the claims

Independent claims 1 and 15 are amended to clarify that the reporter molecule or fluorescent dye is coupled to the aptamer and replaces a nucleic acid residue within the aptamer or is inserted between two residues within the aptamer. These positions are internal and distinct from positioning the reporter molecule or fluorescent dye at the 5'- or 3'-terminal ends of the aptamer (pg. 9, ll. 6-14; pg. 17, ll. 6-9). No new matter has been added.

The 35 U.S.C. §102(a) & (e) rejections

Claims 1, 6-12, 15, 19, 23, 25, and 28 are rejected under 35 U.S.C. §102(a) as being anticipated by **Jayasena** *et al.* (WO 99/31276). Claims 1, 6-12, 15, 19, 23, 25, and 28 are rejected

under 35 U.S.C. §102(e) as being anticipated by **Jayasena** *et al.* (U.S. 6,531,286). Applicant respectfully traverses these rejections.

The specifications, drawings and Abstracts in **Jayasena** *et al.* (WO 99/31276) and **Jayasena** *et al.* (U.S. Patent No. 6,531,286) are identical. As such, in presenting arguments *infra*, Applicant will refer to **Jayasena** *et al.* ('286), particularly in that only this reference is cited herein in a 35 U.S.C. Section 103(a) rejection. Any reference to a specific teaching in **Jayasena** *et al.* ('286) can be found exactly in the corresponding **Jayasena** *et al.* (WO 99/31276).

In considering independent claims 1 and 15, the Examiner states that **Jayasena** *et al.* teach Applicant's method of transducing the conformational change of a signaling aptamer occurring upon binding a ligand to a detectable signal generated by a reporter molecule/fluorescein appended to the aptamer prior to binding. The Examiner also states that fluorescein phosphoramidite is covalently coupled to form the signaling aptamer by replacing a nucleic acid in the aptamer (col. 29, ll. 40-65). The Examiner further states that the signaling aptamer is placed in solution, the ligand contacts the signaling aptamer in solution, the aptamer binds the ligand and thereby changes conformation, and the increase in fluorescence

intensity generated by the reporter molecule/fluorescein upon the conformational change is detected (col. 23, ll. 7-64; Claim 1).

Jayasena *et al.* teach a ligand beacon assay where a molecular beacon is the reporter and nucleic acid ligands are the sensor (Abstract). The molecular beacon sequence contains at least one fluorescent group, e.g., fluorescein synthesized via fluorescein phosphoramidite, and at least one quenching moiety, e.g., DABCYL (col. 18, ll. 23-27; col. 29, ll. 40-48; Fig. 1). The sequence of the molecular beacon contains a loop that is complementary to a nucleic acid ligand that is an aptamer (col. 8, ll. 25-29; Fig. 2A). Although not the preferred embodiment, in comparing **Jayasena** *et al.* to the instant invention, this reference teaches that the the molecular beacon can only hybridize to nucleic acid ligands or aptamers that are bound to their cognate targets and have undergone a conformational change allowing hybridization. This is accompanied by a measurable change in the spectral properties of the molecular beacon (col. 6, ll. 8-13; col. 20; ll. 20-34).

Applicant's invention, as recited in amended claims 1 and 15, comprises a signaling aptamer with a reporter molecule/ fluorescent dye covalently attached therein. Binding of the cognate ligand, or target as in **Jayasena** *et al.*, for the signaling aptamer to

the signaling aptamer transduces a conformational change in the aptamer to an increase in signaling of the reporter/ fluorescent dye covalently attached within the aptamer. **Jayasena** *et al.* specifically teach that the molecular beacon is the reporter molecule (Abstract), the nucleic acid ligand, i.e., the ligand for the molecular beacon, is an aptamer (col. 12, ll. 3-4), the nucleic acid ligand or aptamer changes conformation upon binding its cognate target (col. 20, ll. 24-27) and the molecular beacon can only hybridize to the nucleic acid ligand upon its conformational change and subsequently signal via an increase in fluorescence upon hybridizing (col. 20, ll. 24-31). These teching of **Jayasena** *et al.* are in contrast to Applicant's method.

First, the reporter molecule is not covalently coupled within the nucleic acid ligand or aptamer to form a signaling aptamer nor even is associated therewith prior to the nucleic acid ligand or aptamer binding the target. The molecular beacon can only hybridize with, that is, form ionic bonds with, the nucleic acid ligand.

Secondly, the conformational change that the nucleic acid ligand undergoes upon binding the target does not directly transduce to a change in spectral properties or fluorescence because

the reporter/fluorescent dye does not comprise the nucleic acid ligand or aptamer. The changed conformation itself does not result in a fluorescence increase, but rather induces the molecular beacon to undergo a conformational change and hybridize with the nucleic acid ligand bound to target which is then transduced to a change in fluorescence because the quencher in the molecular beacon is no longer proximate to the fluorescent group.

Finally, the method taught in **Jayasena** *et al.* utilizes a molecular beacon which, as is known in the art and taught in **Jayasena** *et al.* (col. 1, ll. 52-57; Fig. 1), are nucleic acid sequences, folded into stem loops, and containing a fluorophore and a quencher in close proximity in the stem loop configuration. As such, a molecular beacon is not a signaling aptamer. The method, in that a conformational change is transduced to a change in a spectral property, would not work otherwise.

Claims 6-12 and 28 and 19, 23 and 25, depend from amended independent claims 1 and 15, respectively. These dependent claims are drawn to the types of molecules used for the aptamers, reporter molecules and dyes, specific types of signaling aptamers and a method of quantitation using the methods recited in independent claims 1 and/or 15. As these claims depend from

amended independent claims 1 or 15 and further limit recited elements therein or add another method step thereby narrowing the method and as **Jayasena** *et al.* does not anticipate claims 1 and 15, then neither does the inclusion of any or all of claims 6-12 and 28 and 19, 23, 25 and 28 anticipated by **Jayasena** *et al.* ('286).

For a valid §102 rejection, the prior art references must contain each element of the claimed invention. Absent the teaching of covalently coupling the reporter/fluorescent dye within the nucleic acid ligand or aptamer and of transducing the conformational change of the nucleic acid ligand upon binding a cognate target to a direct increase in fluorescence intensity of the reporter molecule/fluorescent dye covalently coupled therein, **Jayasena** *et al.* (U.S. Patent No. 6,531,286) and, by extension, **Jayasena** *et al.* (WO 99/31276), do not anticipate Applicant's claimed invention.

Therefore, as these references are not valid prior art against the instant application under 35 U.S.C. §102 and in view of the preceding amendments and remarks, Applicant respectfully submits that the cited reference does not anticipate claims 1, 6-12, 15, 19, 23, 25, and 28 under 35 U.S.C. §102. Accordingly, Applicant

respectfully requests that the rejection of claims 1, 6-12, 15, 19, 23, 25, and 28 under 35 U.S.C. §102(b) and §102(e) be withdrawn.

The 35 U.S.C. §103(b) rejection

Claims 20-22, and 24 are rejected under 35 U.S.C. §103(a) as being unpatentably obvous over **Jayasena** *et al.* (U.S. 6,531,286) in view of **Szostak** *et al.* (U.S. Patent No. 5,631,146). Applicant respectfully traverses this rejection.

Applicants' invention and **Jayasena** *et al.* ('286) are as discussed *supra*. **Szostak** *et al.* teach single-stranded DNA molecules which bind adenosine or an adenosine-5'-phosphate and methods for producing and isolating them.

Claims 20-22 and 24 depend from amended independent claim 15. Claims 20-22 and 24 limit the aptamers and ligands used in the instant method. As discussed *supra*, Applicants maintain that **Jayasena** *et al.* ('286) do not anticipate the instant invention for, at a minimum, not teaching a signaling aptamer comprising an aptamer having a reporter molecule/fluorescent dye covalently coupled within the aptamer. Thus, further limiting the aptamer to an anti-adenosine RNA aptamer or an anti-adenosine DNA aptamer and the ligand to adenosine, as taught by Szostak *et al.*, can not render the

instant invention obvious. Therefore, the invention as a whole was not obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, Applicant respectfully requests that the rejection of claims 20-22 and 24 under 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed October 27, 2003. If any issues remain, the Examiner is respectfully requested to telephone the attorney of record signing the instant document for immediate resolution. Applicants believe no fees are due, however, should this be in error, please debit any applicable fees from Deposit Account No. 07-1185 upon which the undersigned is allowed to draw.

Respectfully submitted,

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Benjamin Aaron Adler, Ph.D., J.D.
Registration No. 35,423
Counsel for Applicant

ADLER & ASSOCIATES
8011 Candle Lane
Houston, Texas 77071
(713) 270-5391 (tel.)
(713) 270-5361 (facs.)
badler1@houston.rr.com